The preparation of some heteroaromatic and aromatic aldehydes

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Dedicated to Gurnos Jones on the occasion of his 70th birthday  
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Abstract
Heteroaromatic α- and β-carboxaldehydes were prepared by the formylation with DMF of α-lithio benzofuran, benzothiophene, N-methylbenzimidazole and 10-methylphenothiazine obtained by direct lithiation and β-lithio compounds from lithium-bromine exchange. Dialkoxybenzaldehydes were prepared by the formylation of dialkoxybenzenes with hexamethylenetetramine (HMTA) or by the alkylation of dihydroxybenzaldehydes with alkyl bromides or iodides.

Keywords: Heteroaromatic aldehyde synthesis, dialkoxybenzaldehyde synthesis, lithio benzofuran, lithio benzothiophene, formylation, lithium-bromine exchange

Introduction
Heteroaromatic and aromatic aldehydes carrying additional substituents are important as versatile intermediates in the pharmaceutical industry and for organic synthesis in general. Ongoing studies on the synthesis of nitrones1 required the preparation of heteroaromatic aldehydes and dialkoxybenzaldehydes. As the published methods for preparing many of these compounds are frequently low yielding and/or not suitable for large-scale preparation,2 we now report the preparation of heteroaromatic aldehydes by the lithiation-formylation approach and of
dialkoxybenzaldehydes by the formylation of dialkoxy-benzenes or by the alkylation of dihydroxybenzaldehydes.

**Results and Discussion**

**General Procedures.** N-Methylformanilide in the presence of POCl$_3$ has been used for the preparation of heteroaromatic and aromatic aldehydes, but requires that the position of the aromatic ring, at which the formyl group is desired to be introduced, is sufficiently reactive to allow selective formylation. Direct lithiation and subsequent formylation with DMF is a facile procedure used to prepare heteroaromatic aldehydes with the formyl group adjacent to a heteroatom, regioselectively and in good yields. For example, the lithiation of furans/benzofurans$^{4a}$ and benzothiophenes$^{4b}$ always occurs at a free a-position.

**Benzofuran-2-carboxaldehyde (2a), benzothiophene-2-carboxaldehyde (2b) and N-methylbenzimidazole-2-carboxaldehyde (2c).** Bisagni *et al.*, reported that benzofuran-2-carboxaldehyde 2a was prepared in 38% yield by the Vilsmeier formylation of benzofuran 1a with DMF and POCl$_3$. Our work showed that direct lithiation of 1a with n-BuLi, and subsequent formylation with DMF, gave 2a in 67% yield.

Benzothiophene-2-carboxaldehyde 2b was previously synthesized in 62% yield by the lithiation of benzothiophene 1b, followed by the treatment with N-methylformanilide. Use of DMF instead of N-methylformanilide produced 2b in 81% yield.

Le Bris *et al.*$^7$ reported the preparation of N-methylbenzimidazole-2-carboxaldehyde 2c in 50% yield by the SeO$_2$ oxidation of 1,2-dimethylbenzimidazole, however 1,2-dimethylbenzimidazole is very expensive. By using the lithiation-formylation approach, 2c was obtained in 44% yield from N-methylbenzimidazole.

**10-Methylphenothiazine-4-carboxaldehyde (4).** 10-Ethylphenothiazine-4-carboxaldehyde was previously prepared in 69% yield by lithiation of 10-ethylphenothiazine with sec-BuLi and subsequent formylation with DMF.$^8$ However, similar treatment of 10-methylphenothiazine 3 with sec-BuLi and DMF did not afford 10-methylphenothiazine-4-carboxaldehyde 4. Using n-BuLi instead of sec-BuLi as a lithiation reagent gave 4 (40%) together with two further compounds: 3 (12%) and by-product A (22%), which were all isolated by column chromatography (Scheme 1). The GC-MS spectra show that 4 and A are isomeric 10-methylphenothiazine carboxaldehydes with the same molecular weight and expected mass spectra splitting patterns. By-product A was difficult to isolate, because its chromatography characterization is close to that of the starting material 3. The NMR spectrum of a small specimen of A was different from both 10-methylphenothiazine-4-carboxaldehyde and 10-methylphenothiazine-3-carboxaldehyde. Since there are seven aromatic hydrogen peaks overlapped in $^1$H NMR spectrum of A, it is difficult to determine the position of the formyl
group from the splitting patterns of its $^1$H NMR spectrum. Therefore, we believe that A is either 1- or 2-formylated product.

![Chemical structure](image)

**Scheme 1**

**2-Ethylbenzofuran-3-carboxaldehyde (7a) and 2-methylbenzothiophene-3-carboxaldehyde (7b).** Bisagni *et al.* reported that 2-ethylbenzofuran-3-carboxaldehyde 7a was prepared in 66% yield by the Vilsmeier formylation of 2-ethyl-benzofuran 5a with DMF and POCl$_3$, but these conditions in our hands gave a complex mixture. However, bromination of 5a, according to the literature, gave 3-bromo intermediate 6a in 67% yield. Treatment of 6a successively with n-BuLi and DMF gave the desired 2-ethylbenzofuran-3-carboxaldehyde 7a in 78% yield. The bromination of 2-methylbenzothiophene 5b, according to the reported method, gave 3-bromo intermediate 6b, which was converted into 2-methylbenzothiophene-3-carboxaldehyde 7b in 42% yield via lithium-bromine exchange and formylation with DMF (Scheme 2).

Benzothiophene-3-carboxaldehyde 7c was previously prepared in low yield (7%) by direct formylation of benzothiophene with $N$-methylformanilide and POCl$_3$. Campagne *et al.* prepared 7c in 36% yield from expensive 3-methylbenzothiophene in three steps. These reactions are not adaptable for large-scale preparation, as they require peroxide as a reactant and form by-products. According to the literature, bromination of benzothiophene 5c readily gave
3-bromobenzothiophene 6c in 60% yield. However, $^1$H, $^{13}$C NMR spectra show that the formylation of 6c with sec-BuLi and DMF afforded an inseparable mixture due to their close $R_f$ values of benzothiophene-3-carboxaldehyde 7c and benzothiophene-2-carboxaldehyde 2b. The formation of 2b is presumably due to the exchange of benzothiophene-3-carbanion with the active proton at the 2-position, leading to benzothiophene-2-carbanion.

10-Methylphenothiazine-3-carboxaldehyde (9). 10-Methylphenothiazine-3-carboxaldehyde 9 was previously prepared in 60% yield by bromination of 3 with Br$_2$, followed by the subsequent lithium-bromine exchange and formylation with DMF.$^{12}$ We found that bromination of 3 with one equivalent of Br$_2$ gave a mixture of 3, 3-bromo-10-methylphenothiazine 8 and 3,7-dibromo-10-methylphenothiazine with the ratio as 2:3:1 based on the crude $^1$H NMR spectrum. The isolated yield of 8 is 40%. Treatment of 8 with sec-BuLi, and trapping the intermediate with DMF afforded 10-methylphenothiazine-3-carboxaldehyde 9 in 62% yield (Scheme 2).

Scheme 2

Two general methods have been reported for the preparation of dialkoxybenzaldehydes. The first method (method A) involves direct formylation of a dialkoxybenzene with hexamethylenetetramine (HMTA): Duff found that heating phenols with HMTA in glycerol in the presence of glyceroboric acid, followed by an aqueous work up gave salicylaldehyde in rather low yields.$^{13}$ Suzuki employed modified conditions with a stronger acid, such as
methanesulfonic, trifluoroacetic or polyphosphoric acid as a solvent,\textsuperscript{14} which successfully introduced the formyl group onto several electron-deficient aromatic rings.\textsuperscript{15} The second method (method B) involves alkylation of a dihydroxybenzaldehyde with an alkyl halide under basic conditions, e.g., potassium carbonate\textsuperscript{16a-c} or sodium ethoxide \textsuperscript{16d} (Scheme 3).

\[ \text{Method A} \quad \text{Method B} \]

\[
\begin{align*}
\text{HMTA} & \quad \text{RBr} \\
\text{Base} & \quad \text{CHO}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{RBr} \\
\text{HO} & \quad \text{Base}
\end{align*}
\]

\[ ^a \text{Commercially available.} \quad ^b \text{Failed by using either method A or method B.} \quad ^c \text{Original target failed but gave cyclized compound 13.} \quad ^d \text{Original target failed but gave 14 and 15.} \]

Isolated yield (used method) for \textbf{10}, \textbf{11} and \textbf{12}

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<th>\textbf{11}</th>
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<td>ClCH\textsubscript{2}CH\textsubscript{2}</td>
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<td>90 (B)</td>
<td>74 (B)</td>
<td>71 (B)</td>
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\textbf{Scheme 3}

\textbf{Preparation of 2,4-dialkoxybenzaldehydes (10)}. 2,4-Diethoxybenzaldehyde \textbf{10a} was prepared by the reaction of 2,4-dihydroxybenzaldehyde with ethyl iodide in the presence of sodium
ethoxide.\textsuperscript{16d} We prepared 10a in 48\% yield by the formylation of 1,3-diethoxybenzene with HMTA. Similar HMTA formylation of 1,3-diphenoxybenzene afforded novel 2,4-diphenoxybenzaldehyde 10b in 57\% yield. According to the reported procedure,\textsuperscript{16c} 2,4-bis(benzyloxy)benzaldehyde 10c was produced in 67\% yield by the alkylation of 2,4-dihydroxybenzaldehyde with benzyl bromide. A similar alkylation using 1-chloro-2-bromoethane furnished the new compound 2,4-bis(2-chloroethoxy)benzaldehyde 10d in 51\% yield. Faulques et al.\textsuperscript{17} reported the preparation of 2-hydroxy-4-(2-propynyloxy)benzaldehyde by using equimolar 2,4-dihydroxybenzaldehyde and 3-bromo-1- propyne and isolated 2,4-bis(2-propynyloxy)benzaldehyde 10e as a by-product in low yield (7\%). We obtained 10e in 90\% yield with a 2.3:1 molar ratio of 3-bromo-1-propyne to 2,4-dihydroxybenzaldehyde.

**Preparation of 3,4-dialkoxybenzaldehydes (11).** Novel 3,4-bis(2-propynyloxy)benzaldehyde 11e was readily prepared in 74\% yield by the alkylation of 3,4-dihydroxybenzaldehyde with 3-bromo-1-propyne. Attempts to prepare 3,4-diphenoxybenzaldehyde 11b using either method A or method B failed. No 3,4-bis(2-chloroethoxy)benzaldehyde 11d was produced by the alkylation of 3,4-dihydroxybenzaldehyde with ClCH\textsubscript{2}CH\textsubscript{2}Br. The cyclized compound 2,3-dihydro-1,4-benzodioxine-6-carboxaldehyde 13 was always obtained in up to 55\% yield under various condition of reaction temperature and solvent.

**Preparation of 2,5-dialkoxybenzaldehydes (12).** 2,5-Diethoxybenzaldehyde 12a was previously synthesized in 85\% yield by the formylation of 1,4-diethoxybenzene with SnCl\textsubscript{4} and Cl\textsubscript{2}CHOCH\textsubscript{3}.\textsuperscript{18} We found that the HMTA formylation of 1,4-diethoxybenzene gave 12a in 34\% yield. Similar alkylations of 2,5-dihydroxybenzaldehyde with benzyl bromide and 3-bromo-1-propyne furnished the new compounds 12c and 12e in 35\% and 71\% yields, respectively (Scheme 3).

Attempts to synthesize 12d using either method A or method B failed. Formylation of 1,4-diphenoxybenzene with HMTA to 12b introduced the formyl group onto a terminal benzene ring instead of the central benzene ring to give 4-(4-phenoxyphenoxy)benzaldehyde 14 (yield < 10\%) and 4-[4-(4-formylphenoxy)phenoxy] benzaldehyde 15 (yield < 10\%). This is presumably due to the fact that i) the central benzene ring is more hindered than the terminal ones; ii) reaction is easier in the para-position than the ortho-position; iii) the effect of a meta-phenoxy group is possibly deactivating.

In summary, multi-gram scale heteroaromatic 2-carboxaldehydes and 3-carboxaldehydes were prepared by a-lithiation or b-lithium-bromine exchange, followed by the formylation with DMF. Dialkoxybenzaldehydes were prepared either by the formylation of dialkoxybenzene with HMTA or by the alkylation of dihydroxybenzaldehydes with alkyl bromides.
Experimental Section

General Procedures. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Gemini 300 NMR spectrometer (300 MHz and 75 MHz respectively) in CDCl$_3$ (with TMS for $^1$H and CDCl$_3$ for $^{13}$C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument.

General procedure for preparation of 2a-c
To a solution of 1a-c (8.5 mmol) in dry THF (40 mL), was added dropwise n-BuLi (6.0 mL, 1.42 M in hexane) at -78 °C under N$_2$. The mixture was stirred at -78 °C for 1 h and then DMF (1.24 g, 17.0 mmol) was added. After 4 h, the mixture was poured into aqueous HCl (4.5% w/v, 80 mL) and stirred at 0 °C for 0.5 h. The organic phase was separated and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic phase was dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexane/EtOAc as eluent to give 2a-c.

Benzofuran-2-carboxaldehyde (2a). Colorless oil (bp$^5$ 135 °C/18 mmHg); Yield, 67%; $^1$H NMR : $\delta$ 7.31 (t, $J$ = 7.2 Hz, 1H), 7.46-7.57 (m, 3H), 7.72 (d, $J$ = 7.8 Hz, 1H), 9.84 (s, 1H); $^{13}$C NMR : $\delta$ 112.4, 117.7, 123.5, 124.0, 126.4, 129.0, 152.4, 156.0, 179.5. MS (EI): 146 (M, 100), 89 (80), 63 (50).

Benzothiophene-2-carboxaldehyde (2b). Colorless needles; Yield, 81%; mp 34-35 °C (mp$^6$ 34-34.5 °C); $^1$H NMR : $\delta$ 7.37-7.60 (m, 2H), 7.82-7.90 (m, 2H), 7.95 (s, 1H), 10.05 (s, 1H); $^{13}$C NMR : $\delta$ 123.1, 125.1, 126.1, 128.0, 134.4, 138.4, 142.4, 143.1, 184.5.

1-Methyl-1H-benzimidazole-2-carboxaldehyde (2c). Colorless needles; Yield, 44%; mp 110-111 °C (mp$^7$ 110 °C); $^1$H NMR : $\delta$ 4.08 (s, 3H), 7.36-7.45 (m, 3H), 7.87-7.90 (m, 1H), 10.06 (s, 1H); $^{13}$C NMR : $\delta$ 31.0, 110.4, 122.0, 123.8, 126.5, 136.7, 142.4, 145.9, 184.7.

General procedure for preparation of 10-methylphenothiazine-4-carboxaldehyde (4)
To a solution of 10-methyl-10H-phenothiazine 3 (2.0 g, 9.4 mmol) in dry ether (100 mL) was added TMEDA (3.0 mL, 20 mmol), followed by dropwised n-BuLi (6.0 mL, 1.42 M in hexane) at -78 °C under N$_2$. The mixture was stirred at -78 °C for 2 h and DMF (1.24 g, 17.0 mmol) was then added. After 1 h, the mixture was poured into aqueous HCl (4.5% w/v, 80 mL) and stirred at 0 °C for 0.5 h. The ether phase was separated and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic phase was dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent and then recrystallized from EtOAc to give 4 (0.9 g, 40%). Yellow needles; mp 110-111 °C; $^1$H NMR : $\delta$3.29 (s, 3H), 6.74 (d, $J$ = 8.1 Hz, 1H), 6.85-6.93 (m, 2H), 7.09-7.22 (m, 3H), 7.37 (d, $J$ = 6.9
Hz, 1H), 10.23 (s, 1H); $^{13}$C NMR: $\delta$ 35.6, 114.1, 118.4, 122.1, 122.6, 124.4, 126.7, 127.1, 127.9, 128.8, 132.5, 145.6, 146.3, 190.2. Anal. Calcd for C$_{14}$H$_{11}$NSO: C, 69.68; H, 4.59; N, 5.80. Found: C, 70.01; H, 4.64; N, 5.86.

**General procedure for preparation of 7a, 7b and 9**

Sodium hydroxide (4.9 g, 123 mmol) was dissolved in glacial acetic acid (300 mL) under N$_2$. The compound 5a, 5b or 3 (40 mmol) was added, followed by chloroform (50 mL). Bromine (6.7 g, 40 mmol) in glacial acetic acid (40 mL) was added dropwise during 2 h at 5-10 $^\circ$C. The suspension was stirred at room temperature for 2 h and then evaporated to dryness. The residue was dissolved in 10% NaHCO$_3$ and CH$_2$Cl$_2$. The aqueous phase was separated and extracted with CH$_2$Cl$_2$. The combined organic phase was dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent to give 6a, 6b or 8.

To a solution of the intermediate 6a, 6b or 8 (6.0 mmol) in dry THF (40 mL), was added dropwise s-BuLi (5.4 mL, 1.1 M in hexane) at -78 $^\circ$C under N$_2$. The mixture was stirred at -78 $^\circ$C for 1 h and DMF (0.44 g, 6.0 mmol) was then added. After 1 h, the mixture was poured into aqueous HCl (4.5% w/v, 80 mL) and stirred at 0 $^\circ$C for 0.5 h. The THF phase was separated and the aqueous phase was extracted with CH$_2$Cl$_2$. The combined organic phase was dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent to give 7a, 7b or 9.

3-Bromo-2-ethylbenzofuran (6a). Colorless oil; Yield, 67%; $^1$H NMR: $\delta$ 1.30 (t, $J = 7.5$ Hz, 3H), 2.80 (q, $J = 7.5$ Hz, 2H), 7.20-7.30 (m, 2H), 7.35-7.50 (m, 2H); $^{13}$C NMR: $\delta$ 11.9, 20.2, 93.4, 111.0, 119.1, 123.0, 124.3, 128.4, 153.4, 156.6. MS (EI): 226 (40), 224 (40), 209 (100), 207 (100).

3-Bromo-2-methylbenzothiophene (6b). Colorless oil; Yield, 70%; $^1$H NMR: $\delta$ 2.49 (s, 3H), 7.26-7.40 (m, 2H), 7.66-7.70 (m, 2H); $^{13}$C NMR: $\delta$ 15.4, 110.8, 116.7, 121.6, 124.3, 124.5, 125.0, 153.7, 171.4, 184.7. MS (EI): 174 (M, 100), 159 (45), 145 (40), 131 (50), 115 (30).

2-Ethylbenzofuran-3-carboxaldehyde (7a). Colorless oil; Yield, 78%; $^1$H NMR: $\delta$ 1.41 (t, $J = 7.5$ Hz, 3H), 3.10 (q, $J = 7.5$ Hz, 2H), 7.29-7.32 (m, 2H), 7.42-7.45 (m, 1H), 8.10-8.13 (m, 1H), 10.20 (s, 1H); $^{13}$C NMR: $\delta$ 12.6, 20.5, 110.8, 116.7, 121.6, 124.3, 124.5, 125.0, 153.7, 171.4, 184.7. MS (EI): 174 (M, 100), 159 (45), 145 (40), 131 (50), 115 (30).

2-Methyl-benzothiophene-3-carboxaldehyde (7b). Colorless oil; Yield, 42%; $^1$H NMR: $\delta$ 2.82 (s, 3H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.41 (t, $J = 7.5$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 8.54 (d, $J = 8.1$ Hz, 1H), 10.27 (s, 1H); $^{13}$C NMR: $\delta$ 14.1, 121.4, 123.5, 125.0, 125.7, 129.8, 136.6, 137.1, 157.6, 184.2. Anal. Calcd for C$_{10}$H$_{8}$OS: C, 68.15; H, 4.58. Found: C, 68.06; H, 4.47.

10-Methylphenothiazine-3-carboxaldehyde (9). Colorless needles; Yield, 62% (based on 8); mp 86-87 $^\circ$C (mp$^{12}$ 86-87 $^\circ$C); $^1$H NMR: $\delta$ 3.34 (s, 3H), 6.74-6.79 (m, 2H), 6.94-6.97 (m, 1H),
7.06- 7.14 (m, 2H), 7.52- 7.59 (m, 2H), 9.74 (s, 1H); $^{13}$C NMR : $\delta$ 35.6, 113.5, 114.7, 122.3, 123.4, 123.7, 127.1, 127.6, 130.3, 130.9, 143.8, 150.8, 189.9.

General procedure for the preparation of dialkoxybenzaldehydes

Method A. A mixture of an appropriate dialkoxybenzene (40 mmol) and HMTA (12.8 g, 92 mmol) in the solvents (given below) was heated to reflux for 3 h. After cooling, the mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water, dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography with hexane/EtOAc (6:1) as eluent to give the dialkoxybenzaldehyde. Formylation of 1,4-diphenoxybenzene with HMTA gave 14 and 15 instead of the desired compound 12b.

2,4-Diethoxybenzaldehyde (10a). (CH$_3$COOH/H$_2$O = 100/20 mL); Colorless needles; Yield, 48%; mp 69-70 °C (mp$^{16}$ 68-71 °C); $^1$H NMR : $\delta$ 1.40-1.48 (m, 6H), 4.04-4.12 (m, 4H), 6.40 (s, 1H), 6.49 (d, $J = 8.7$ Hz, 1H), 7.78 (d, $J = 8.7$ Hz, 1H), 10.31 (s, 1H); $^{13}$C NMR : $\delta$ 14.4, 14.5, 63.8, 63.9, 98.7, 106.1, 118.7, 130.0, 163.0, 165.4, 188.2.

2,4-Diphenoxybenzaldehyde (10b). (CF$_3$COOH/CH$_3$COOH = 130/130 mL); Colorless needles; Yield, 57%; mp 52-53 °C; $^1$H NMR : $\delta$ 6.46 (s, 1H), 6.65 (d, $J = 6.7$ Hz, 1H), 7.00-7.18 (m, 6H), 7.31-7.39 (m, 4H), 7.88 (d, $J = 8.7$ Hz, 1H), 10.39 (s, 1H); $^{13}$C NMR : $\delta$ 106.8, 111.9, 119.4, 120.2, 121.8, 124.5, 124.9, 130.0, 130.04, 130.2, 54.7, 155.8, 161.7, 164.1, 187.8. Anal. Calcd for C$_{19}$H$_{14}$O$_3$: C, 78.60; H, 4.87. Found: C, 78.97; H, 4.87.

2,5-Diethoxybenzaldehyde (12a). (CF$_3$COOH/CH$_3$COOH = 30/90 mL); Yield, 34%; mp 61-62 °C (mp$^{18}$ 60-61 °C); $^1$H NMR : $\delta$ 1.36-1.46 (m, 6H), 4.00 (q, $J = 6.9$ Hz, 2H), 4.09 (q, $J = 6.9$ Hz, 2H), 6.91 (d, $J = 9.0$ Hz, 1H), 7.05-7.11 (m, 1H), 7.29 (d, $J = 3.0$ Hz, 1H), 10.46 (s, 1H); $^{13}$C NMR : $\delta$ 14.6, 63.9, 64.7, 110.8, 114.3, 123.9, 125.0, 152.7, 156.0, 189.6.

4-(4-Phenoxophenyl)benzaldehyde (14). (CF$_3$COOH/CH$_3$COOH = 60/50 mL); Colorless needles; Yield, < 10%; mp 47-48 °C (mp$^{19}$ 46-48 °C); $^1$H NMR : $\delta$ 7.02-7.14 (m, 9H), 7.33-7.38 (m, 2H), 7.85 (d, $J = 8.7$ Hz, 2H), 9.91 (s, 1H). $^{13}$C NMR : $\delta$ 117.1, 118.7, 120.3, 121.8, 123.4, 129.8, 131.1, 131.9, 150.3, 154.2, 157.1, 163.5, 190.7.

4-[4-(4-Formylphenoxophenoxy)]benzaldehyde (15). Colorless needles; Yield, < 10%; mp 157-158 °C (mp$^{19}$ 157-158 °C); $^1$H NMR : $\delta$ 7.08 (d, $J = 8.2$ Hz, 4H), 7.14 (s, 4H), 7.86 (d, $J = 8.2$ Hz, 4H), 9.94 (s, 2H). $^{13}$C NMR : $\delta$ 117.5, 122.0, 131.4, 132.0, 151.8, 163.0, 190.6.

Method B. An appropriate dihydroxybenzaldehyde (20 mmol) was mixed with an alkyl bromide (46 mmol) in the presence of K$_2$CO$_3$ (anhydrous, 14 g). The reaction temperature, time and solvent are given below. After cooling, the mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water, dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography with hexane/EtOAc (3:1) as eluent to give the dialkoxybenzaldehyde. Alkylation of 3,4-dihydroxybenzaldehyde with ClCH$_2$CH$_2$Br gave 13 instead of the desired compound 11d.
2,4-Bis(benzyloxy)benzaldehyde (10c). (Reflux, 6 h; BuOH 30 mL); Colorless needles; Yield, 67%; mp 87-88 °C (mp\textsuperscript{16c} 87-88 °C); \textsuperscript{1}H NMR : δ 5.05 (s, 2H), 5.08 (s, 2H), 6.57 (s, 1H), 6.59 (d, J = 8.3 Hz, 1H), 7.34-7.38 (m, 10H), 7.81 (d, J = 8.3 Hz, 1H), 10.37 (s, 1H); \textsuperscript{13}C NMR : δ 70.2, 99.9, 106.9, 119.3, 127.2, 127.4, 128.15, 128.2, 128.6, 130.3, 135.8, 162.6, 165.1, 188.0.

2,4-Bis(2-chloroethoxy)benzaldehyde (10d). (reflux, 20 h; CH\textsubscript{3}COCH\textsubscript{3} 60 mL); Colorless needles; Yield, 51%; mp 80-81 °C; \textsuperscript{1}H NMR : δ 3.82-3.90 (m, 4H), 4.28-4.34 (m, 4H), 6.47 (s, 1H), 6.57 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 10.35 (s, 1H); \textsuperscript{13}C NMR : δ 41.5, 68.2, 68.4, 99.7, 106.6, 119.7, 130.4, 162.1, 164.4, 187.9. Anal. Calcd for C\textsubscript{11}H\textsubscript{12}O\textsubscript{3}: C, 50.21; H, 4.61. Found: C, 50.22; H, 4.58.

2,4-Bis(2-propynyloxy)benzaldehyde (10e). (80 °C, 2.5 h; DMF 80 mL); Colorless needles; Yield, 90%; mp 110-114 °C (mp\textsuperscript{18} 110 °C); \textsuperscript{1}H NMR : δ 3.16 (s, 1H), 3.17 (s, 1H), 4.84 (s, 2H), 4.90 (s, 2H), 6.69 (d, J = 8.6 Hz, 1H), 6.78 (s, 1H), 7.73 (d, J = 8.6 Hz, 1H), 10.23 (s, 1H); \textsuperscript{13}C NMR : δ 55.8, 56.2, 77.5, 77.6, 77.8, 100.1, 107.5, 119.1, 129.5, 161.0, 163.3, 187.0.

3,4-Bis(2-propynyloxy)benzaldehyde (11e). (80 °C, 2.5 h; DMF 80 mL); Colorless needles; Yield, 74%; mp 105-106 °C; \textsuperscript{1}H NMR : δ 3.59 (s, 2H), 4.93 (s, 2H), 4.97 (s, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.55 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 9.87 (s, 1H); \textsuperscript{13}C NMR : δ 56.2, 56.4, 78.7, 78.9, 79.1, 112.0, 113.4, 126.7, 130.3, 147.3, 152.3, 191.7. Anal. Calcd for C\textsubscript{13}H\textsubscript{10}O\textsubscript{3}: C, 72.88; H, 4.71. Found: C, 73.12; H, 4.71.

2,5-Bis(benzyloxy)benzaldehyde (12c). (Reflux, 6 h; BuOH 30 mL); Colorless needles; Yield, 35%; mp 89-91 °C; \textsuperscript{1}H NMR : δ 5.01 (s, 2H), 5.10 (s, 2H), 6.97 (d, J = 9.1 Hz, 1H), 7.13-7.17 (m, 1H), 7.30-7.43 (m, 11H), 10.50 (s, 1H); \textsuperscript{13}C NMR : δ 70.5, 71.1, 111.5, 114.9, 124.1, 125.4, 127.3, 127.5, 128.0, 128.2, 128.5, 128.6, 136.2, 136.5, 152.9, 155.8, 189.3.

2,5-Bis(2-propynyloxy)benzaldehyde (12e). (80 °C, 2.5 h; DMF 80 mL); Colorless needles; Yield, 71%; mp 91-92 °C; \textsuperscript{1}H NMR : δ 4.28 (d, J = 4.2 Hz, 2H), 4.31 (d, J = 4.1 Hz, 2H), 6.95 (d, J = 8.8 Hz, 1H), 7.37-7.39 (m, 2H), 9.80 (s, 1H); \textsuperscript{13}C NMR : δ 63.9, 64.5, 117.6, 118.1, 124.0, 130.4, 143.8, 149.1, 190.5.

2,3-Dihydro-1,4-benzodioxine-6-carboxaldehyde (13). (reflux, 2-6 h; DMF or CH\textsubscript{3}COCH\textsubscript{3} 60 mL); Colorless needles; Yield, 55%; mp 51-52 °C (mp\textsuperscript{20} 50-51 °C); \textsuperscript{1}H NMR : δ 4.28 (d, J = 4.2 Hz, 2H), 4.31 (d, J = 4.1 Hz, 2H), 6.95 (d, J = 8.8 Hz, 1H), 7.37-7.39 (m, 2H), 9.80 (s, 1H); \textsuperscript{13}C NMR : δ 63.9, 64.5, 117.6, 118.1, 124.0, 130.4, 143.8, 149.1, 190.5.
References